National Institute of Mental Health

# Challenges in Preventing Relapse in Major Depression

## Summary of a National Institute of Mental Health Workshop on State of the Science of Relapse Prevention in Major Depression

On May 21 and 22, 2001, NIMH convened a workshop on preventing relapse in major depression, as a part of a larger effort to find treatments that can produce durable long-term recovery. Researchers considered definitional and developmental perspectives on depression relapse, the neurobiological and psychological risk factors for episode return, and the prophylactic potential of current treatments and their cost effectiveness.

*NIMH Program Staff Note: While the meeting included several descriptions of efforts to study approaches to relapse and recurrence prevention in community settings such as primary care, the NIMH strongly encourages investigators to develop and test prevention efforts with community populations, and in particular, traditionally underserved populations.*

### Definitions

Participants began by considering the definition of relapse. Definitions of response, remission, relapse, recovery and recurrence, which employ both duration- and severity-based operational criteria, have been critical in tracking illness course and identifying treatment targets.[1,2] However, participants agreed that categorical models of depression may inadequately describe partial treatment response[3] and residual dysfunction. To address this, additional terms such as incomplete recovery as defined by symptom criteria have been proposed. [4] Participants discussed additional terms that could improve understanding of incomplete treatment, and in turn, lead to new treatment strategies.

### Epidemiology of Depression Relapse

There is limited information on whether demographic characteristics of gender or social class affect relapse prevention rates. While females have a higher prevalence of depression beginning in adolescence through later mid-life, it is not known whether life stage and/or gender interact with biomedical or psychosocial factors to affect risk of depression relapse. Estimates from clinical populations indicate that patients with major depression will experience an average of four lifetime episodes of 20 weeks each in duration,[5] but risk may vary by the number of prior depressive episodes. Those with at least 3 prior episodes show 70-80% relapse rates, compared to those with no depression history who show 20-30% rates. Thus, determining number of past episodes remains one of the most reliable predictors of future depression.

Children and Adolescents. Community-based studies indicate that children and adolescents experience continuity of symptoms, if not disorder, from early to later adolescence.[6,7,8,9] Risk factors for onset identified in these studies included: parental depression and social anxiety for

both genders, and poor peer relations for males. Data are limited, but clinic-based and community samples suggest a relapse rate of between 46%[10] and 63%.[11,12,13] These rates should be interpreted cautiously, however, as these studies have had limited period of follow-up, and recurrence and chronicity rates by mid-adulthood are not yet known.

Older Adults. As with the literature on youth, data on the general epidemiology, and relapse risk post treatment in late-life depression are limited. According to community-based studies, late onset depression is more weakly associated with familial risk than midlife onset.[14] Data from acute treatment trials and a few maintenance trials indicate that dosing comparable to acute treatment appears most effective in preventing relapse. Quality of recovery tends to be brittle, with high rates of relapse compared to midlife samples. [15] Late-life depression can be exacerbated by co-occurring medical illness and possible prodromal dementia,[16]suggesting that combination treatments (e.g. psychoeducation, psychostimulants) may be needed for relapse prevention strategies for subgroups of depressed older adults with such comorbid conditions.

Comorbidities. Risk for relapse for patients with anxiety disorders and alcohol dependence comorbid with depression are higher than for depression alone.[9] When another diagnosis precedes depression, the relapse risk is higher, for example when depression occurs secondary to PTSD.[17] Data on relapse with comorbid Axis II disorders are limited. Though personality disorders (PD) are frequently cited as increasing risk for relapse and poor recovery, varying definitions of PD make comparisons between studies difficult. Patients with severe PD are also typically excluded from depression treatment trials.

Personality factors likely contribute to chronicity, relapse and recurrence through neuroticism, which can amplify anxiety, shame and interpersonal sensitivity. Neuroticism has been found to be a robust predictor of quick relapse and slow recovery, even when controlling for baseline depression.[18] Evidence suggests that high neuroticism may be associated with selective recall of negative experiences, and increased attentional allocation to dysphoric moods.[19]

Relapse Prevention among Ethnic Minority Groups. Fewer than 8% of the participants in clinical treatment trials are ethnic minorities, though such groups constitute 30% of the US population.[20] Thus, estimates of relapse rates of depression for ethnic minorities are not available. There are a number of issues to consider in working to reduce such disparities in mental health research and services. Ethnic minority populations are increasingly diverse. African Americans in the community have rates similar to whites, while rates of depression vary by acculturation for other groups. Barriers to health care and clinical research include lower rates of insurance, fewer minority providers, institutional racism, limited knowledge of effective treatments, lack of trust in and concern about appropriate care, and limited access to childcare and transportation. Recent studies indicate hope for future efforts in reducing disparities, inasmuch as Hispanic and African Americans have shown equal or better responses to depression treatments compared to whites.[21,22]

Discussions of efforts to reduce health disparities also considered research on help-seeking behavior in the context of HIV testing among low-income women. Increased knowledge regarding help seeking behavior was considered critical for initial detection and acute treatment of depression, as well as understanding what motivates individuals to return to treatment when

they relapse or experience a reoccurrence. Message framing has been studied with regard to whether recruitment should focus on costs or benefits.[23] The implications for relapse prevention would be to consider how participants construe relapse prevention: Whether in terms of low cost, relative uncertainty, low risk behavior, and optimistic outcomes (gain frame), or as related to high cost, relative uncertainty, high risk, and pessimistic outcomes (loss frame). Once the individual is in treatment, these frameworks could be used within treatment paradigms, such as increasing adherence through gain framed approaches, or addressing frame perceptions that developed from prior experiences with negative side effects or ineffective treatments.

Rates, Risk Factors and Illness Patterns in Less Selected Samples. Many data on relapse/recurrence are based on patients in specialty care, a sample that may overrepresent those more at risk for relapse and poor recovery. Major depression treated in primary care may be milder, with relapse rates estimated at half of those in specialty care.[24] If this is indeed the case, there are a number of public health issues that can be raised. These include issues related to the actual numbers of individuals who might be reached through speciality versus primary care; their degree of depression severity and need for acute and ongoing treatments, and to what degree does the type or quality of treatment affect the efficiency of treatment in both of these care settings. For example, one question that could be posed is whether less intensive treatment resources could target a greater number of less disturbed patients (primary care) and provide a larger public health benefit, relative to a smaller group of more severe patients with more persistent illness (specialty care), who will receive more intensive treatment. Alternatively, to what degree could treatment in primary care be improved to be more efficient?

There are numerous challenges to improving treatment in primary care. Like specialty care, those patients treated in primary care tend to be female, with 50% of first episodes occurring prior to age of 20, suggesting that providers are likely to see patients with prior episodes. Barriers within primary care to providing adequate treatment and follow-up include inadequate assessment, limited availability of psychoeducation and psychosocial support, and limited access to specialists for consultation. Suboptimal doses of antidepressants, and little or no follow-up, likely contribute to a roughly 30% relapse rate.[25] Data collected from primary care settings presented at the meeting suggested that incomplete recovery better predicted long-term outcomes than baseline severity. Research focusing on interventions to reduce relapse in primary care should be acceptable, accessible and affordable, and should address treatment adherence. Finally, cost-effectiveness of relapse prevention efforts must be examined, preferably taking into account system allocation effects.[26]

**Treatment and Prevention Strategies**

The most widely used strategy for preventing depressive relapse is the continuation of the treatment that achieved acute phase remission. Effective maintenance antidepressant therapy can reduce relapse rates by up to 50%.[27,28] Short-term psychotherapies such as Cognitive Behavioral Therapy (CBT) and Interpersonal Therapy (IPT) modified for use after remission is achieved also protect against relapse. CBT with continuation psychotherapy significantly reduced relapse compared to CBT without continuation.[29] Patients with earlier initial onset and with less robust

remission showed even greater reductions. Similar findings have been reported for continuation phase IPT.[30]

New strategies have focused on using specific treatments for different phases of depression, that is, switching patients to a different therapy after acute phase remission is achieved. Examples include following antidepressant medication with CBT[31] and starting nortriptyline after discontinuing ECT.[32]

While the number of studies examining the effectiveness of cross-over algorithms is small, the general trend reported is positive. Four RCTs [3, 31, 33, 34]found that CBT-based preventative interventions sequenced with antidepressants provided comparable relapse protection to continuation pharmacotherapy. One study[30] did not find this for IPT vs. maintenance pharmacotherapy, although IPT was significantly more effective compared to maintenance medication in which an active drug was replaced with placebo. Thus, multiple interventions may be more effective at relapse prevention than simply continuing single interventions. Further study is needed, especially in light of the undertreatment of depression in nonspecialty settings.[25]

Continuation treatments may be indicated for subgroups of depressed patients. Specifically, patients with earlier onset and greater chronicity, those with more than two episodes, and those with incomplete response to acute phase intervention are at highest risk, suggesting that tailoring and testing treatments specific to these groups may be indicated. Some workshop participants were more cautious about endorsing the need for continuation treatments, while emphasizing the value of enhancing acute treatment outcomes. A number of studies, including those testing sequencing approaches, indicate a relapse preventative effect when a complete or robust acute phase recovery is achieved,[35,36] consistent with observations that incomplete recovery increases risk of relapse.

The need to determine the active ingredients in effective treatments, as well as designing preventative treatments that can be provided to recovered patients, regardless of type of acute treatment, were also highlighted. For example, Mindfulness Based Cognitive Therapy (MBCT)[33]**,** a therapy provided during recovery that teaches patients to disengage from cognitions linked to relapse, has shown effectiveness, particularly among patients with 3 or more episodes.

**Basic Science and Markers of Relapse Risk**

Research to date has focused on relapse risk factors that are largely clinical features of depression. For example, number of past depressive episodes, quality of remission, and psychiatric comorbidity are the most reliable and robust predictors of relapse to date. Thus, this raises the challenge as to whether such high-risk patients can be identified and treated accordingly. Participants also stressed that identifying markers of relapse risk is vital to treatment development.[37] Basic science paradigms could be used to model relapse processes, especially in searching for mechanisms thought to mediate symptom return. Embedding tests of these models into ongoing prevention trials could provide direct, outcomes-based data to measure the effect of modifying these factors.

Cognitive models of relapse vulnerability have tested predictions derived from Teasdale's Differential Activation Hypothesis,[38] which suggests that risk of severe, persistent depression depends in part of information processing patterns activated during mild dysphoric states. Those who have experienced, in conjunction with depression, events interpreted in themes of severe loss, self-denigration, and hopelessness become predisposed to the reactivation of these cognitions during later periods of dysphoria. Thus, current experiences become more likely to trigger depressive cognition, though during non-depressed periods the affected individuals may not show such thought patterns.

Empirical studies of this model commonly use laboratory-based challenges to induce transient dysphoric mood in groups at high and low relapse risk. As hypothesized, formerly depressed subjects had a more depressogenic cognitive style when feeling sad, but were comparable to low-risk subjects during times of euthymia (see Ingram[19] for a review). Segal and colleagues[38] reported that the degree of laboratory mood-linked cognitive reactivity significantly predicted relapse up to 30 months later. These are among the first clinical data suggesting that challenges in cognitive processing arising from the experience of dysphoria can predict symptom return.

With regard to findings on the neurobiology of relapse, new research is underway on changes in regional brain activation following successful treatment of depression is developing. To date, there are no biological markers predicting relapse vulnerability during maintenance treatment. Recent neuroimaging studies describe frontal and cingulate metabolic abnormalities in depression, with striatal and amygdala-hippocampal changes also noted. Medication seems to normalize these changes, and some change may occur with structured psychological treatment.[39,40,41] Mayberg et al.[42] studied concordant and functional change after provocation of sadness in healthy volunteers and resolution of chronic dysphoria in depressed patients. With sadness, increases in limbic-paralimbic blood flow and decreases in neocortical regions were identified. With depression remission, the reverse was seen. Data showed a significant inverse correlation between subgenual cingulate and right dorsolateral prefrontal activity in both conditions. The presence and maintenance of functional reciprocity between these regions may mediate the relationship between mood and attention seen in normal and pathological conditions. These areas may also be implicated in the amplification of transient dysphoric mood into depressed states.

**Summary and Research Directions**

Depression is disabling, recurrent, and potentially chronic. Acute treatments for depression, although effective, often do not prevent later impairment for many depressed patients due to residual symptoms or relapse. Participants identified specific research challenges that have the potential to effect a more durable recovery and relapse prevention in depression.

Regarding definitions, participants suggested broadening the scope of the relapse construct to reflect differences in the quality and severity of relapse. Outcomes such as level of inter-episode functioning, inter-episode duration, degree of subsyndromal depression without relapse, and level of interpersonal disruption are not captured in current definitions and are rarely analyzed. Yet these likely represent significant quality-of-life effects in patients suffering the return of

subsyndromal symptoms. Similarly, consistency in definitions of treatment, initiation, adherence and tapering approaches across studies would improve analyses of cross-study effectiveness.

Treatment strategies could be refined, tailored for individual characteristics and specific phases of treatment (e.g. acute, continuation, maintenance) depression. With regard to individual characteristics, it would be useful to address patient illness history (e.g., those 3 or more episodes), treatment history (e.g. treatment naïve populations vs. patients who have had multiple, suboptimal medication trials), comorbidity (e.g. personality disorder) and individual treatment preferences (e.g., for IPT, due to focus on relationship problems).

Testing which treatments are effective for which phases of depression, both for their initial effects and the effects that they may have on treatments later in the sequence, would be beneficial. Certain sequenced approaches are apt to be more effective for certain subgroups. Given the long duration of treatment for some, it will be important to understand the role of patient preference, values, and ability to "self-manage" in developing a sequenced treatment strategy with sufficient adherence, and the degree to which these efforts are cost effective.

Further examination is required to link biological and psychological markers to relapse vulnerability. If interventions can be improved by targeting known mediators of relapse, can these markers serve as targets for prevention? Clinical prevention trials can be useful by providing a context in which to test the validity of possible relapse mediators. Assessing patients in these trials for the presence of, and changes in, relapse vulnerability markers would provide direct, outcomes-based data to gauge the protective value of ongoing treatment in modifying these markers.

Also relevant to the science of relapse prevention are larger questions for psychiatric research. Given time and budget limits, what methodological innovations would improve efficacy of longitudinal studies? Further consideration of the ethics and safety of medication withdrawal, rescue procedures, and understanding of long-term risks and benefits of certain treatment strategies, is also needed.

Zindel Segal, Jane Pearson, and Michael Thase organized the workshop. Greg Siegle produced a written record of the meeting. Virginia Lindahl assisted Jane Pearson and Zindel Segal in developing this summary.

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